Applicants respectfully draw the Examiner's attention to Claim 2, where the method of Claim 1 further comprises testing the candidate variant protein for altered immunogenicity relative to the target protein. See Specification at page 34, lines 6-13 and page 56, lines 8-15.

B. The Office Action notes that Claim 1 is indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention because it recites "immunogenicity filter."

As stated in the MPEP §2173.05(a):

> The meaning of every term used in a claim should be apparent from the prior art or from the specification and drawings at the time the application is filed. Applicants need not confine themselves to the terminology used in the prior art, but are required to make clear and precise the terms that are used to define the invention whereby the metes and bounds of the claimed invention can be ascertained. During patent examination, the pending claims must be given the broadest reasonable interpretation consistent with the specification. *In re Morris*, 127 F.3d 1048, 1054, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997); *In re Prater*, 415 F.2d 1393, 162 USPQ 541 (CCPA 1969). See also MPEP § 2111 - § 2111.01. When the specification states the meaning that a term in the claim is intended to have, the claim is examined using that meaning, in order to achieve a complete exploration of the applicant's invention and its relation to the prior art. *In re Zletz*, 893 F.2d 319, 13 USPQ2d 1320 (Fed. Cir. 1989).

In reviewing a claim for compliance with 35 U.S.C. §112, the Examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required (See MPEP §2173.02). If the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is precise as the subject matter permits, the statute demands no more.

Applicants respectfully submit the Examiner has mischaracterized the term "immunogenicity filter." The application defines a "computational immunogenicity filter" as "any one of a number of scoring functions derived from data on binding of peptides to MHC molecules, or T cell epitopes or B cell epitopes." The term "computational immunogenicity filter" is used in the specification and claims to define this point. Additionally, the Specification discloses that, "[t]hese scoring functions are used to rescore the set of primary library sequences to eliminate potentially immunogenic sequences, or eliminate non-immunogenic sequences." Specification at page 30, lines 15-21. See also, Specification at page 4, lines 29-33; page 5, lines 11-15; page 6, lines 31-37; page 7, lines 1-23; page 31, lines 1-19; and pages 32-34.

C. The Office Action points out that it is not clear how the step of optimizing for a scoring function addressed in claims 6-8 is related to step c) of the base claim 1. Applicants respectfully submit that the

"optimization" is relative to steps a) and b), not c). A computational method (e.g. PDA®) technology is used first to identify the sequence having the lowest immunogenic profile. See Specification at page 20, lines 4-19; page 30, lines 1-6 and page 29, lines 26-31. See for example, US Patent Nos. 6,269,312 and 6,403,312. Step c) determines the up or down regulation of immunogenicity. See page 30, lines 15-21.

In light of the foregoing arguments, Applicants respectfully request the reconsideration and withdrawal of the rejection of Claims 1-17 under 35 USC §112, second paragraph.

Claim Rejection 35 USC §112, First Paragraph

Claims 1-17 are rejected under §112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Examiner states that the Specification does not disclose an example of the operability of the method either *in silico* or under experimental conditions on a real protein synthesized following *in silico* design and fail to meet the written description provision, and thus fail to support the genus encompassed by the instant claims.

The Revised Interim Guidelines for the Examination of Patent Applications Under the 35 USC 112, first paragraph "Written Description Requirement," Federal Register, Vol. 64, No. 244, pp 71427-71440, 71436 (Tuesday, December 21, 1999) state:

> "An applicant may also show that an invention is complete by disclosure of sufficiently detailed relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention. [39] i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.[40] What is conventional or well known to one skilled in the art need not be disclosed in detail. [41]. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met."
>
> ..."For each claim drawn to a genus; for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction practice ..., reduction to drawings..., or by disclosure of relevant identifying characteristics, i.e., Structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus." "Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces."

> ..."A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the Examiner to rebut the presumption. The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The examiner has the initial burden of presenting evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. In rejecting a claim, the examiner must set forth express findings of fact regarding the above analysis which support the lack of written description conclusion. These findings should: 1) identify the claim limitation at issue; and 2) establish a prima facie case by providing reasons why a person skilled in the art at the time the invention was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed."
>
> "There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed." In re Wertheim, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976). MPEP 2163(I)(A) "If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met. See, e.g. Vas-Cath, 935 F.2d at 1563, 19 USPQ2d at 1116; Martin v. Johnson, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972)." MPEP §2163 (II)3a

Additionally, "[a]n applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.* 107F3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). MPEP §2163.

In *Vas-Cath Inc. v. Mahurkar* (19USPQ2d 1111, 1116), the court stated, "A fairly uniform standard for determining compliance with the "written description" requirement has been maintained throughout[.]" citing *In re Gosteli.* "Although [the applicant] does not have to describe exactly the subject matter claimed,... the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed.Cir. 1989). The Vas-Cath court went on to state that: "The applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*" *Vas-Cath Inc. v. Mahurkar* (19USPQ2d 1111, 1117).

Applicants submit that the invention as filed is complete by disclosure of sufficiently detailed relevant identifying characteristics, which provide evidence that Applicants were in possession of the claimed invention by disclosing other physical and/or chemical properties, functional characteristics and is coupled with a known or disclosed correlation between function and structure, or some combination of

such characteristics. See Specification at page 7, lines 14-24 and lines 25-32; beginning on page 7, line 34, ending on page 8, line3; page 23, lines 1-5; page 22, lines 29-37; page 31, lines 1-19 and lines 21-29; and page 32, lines 15-24. It is well known to those skilled in the art that a protein sequence may be optimized using computational methods. See Specification at page 20, lines 4-19; page 30, lines 1-6 and page 29, lines 26-31. See for example, US Patent Nos. 6,269,312 and 6,403,312. Furthermore, one skilled in the art would understand that modifying known epitopes affects immunogenicity and as the Examiner has correctly acknowledged on page 6 of the present Office Action that there are numerous publications describing computerized algorithms to predict binding of peptides to MHC molecules. Specification at page 7, lines 14-23 - page 33, lines 4-19.

With regard to the cited case, *Fiers v. Revel*, 25 USPQ2d 16011, 1606(CAFC1993), the Applicants respectfully point out that the cases may be distinguished from the instant case because the reference spoke to the written description requirement regarding DNA or nucleic acid sequences due to the degeneracy of the genetic code. In contrast, the present invention is directed to a method for modulating the immunogenicity of proteins' amino acid sequences.

In light of the foregoing, the Examiner has not made a *prima facie* showing that one skilled in the art would not have recognized the Applicants were in possession of the invention at the time the application was filed. Applicants respectfully request the reconsideration and withdrawal of the written description requirement rejection.

Claim Rejection 35 USC §102 and 103

Claims 1-17 are rejected under 35 USC §103(a) as obvious over Fleckenstein et al or Abrams et al in view of Altuvia et al, Meister et al, or Buus et al and in further view of Mayo et al (WO/98/47089 and US 6,269,312). Each reference will be addressed in turn below.

For rejections under §102, "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)."

The Office Action states Fleckenstein et al teaches a "method for determining peptides with modulated immunogenicity (i.e., with altered binding to leu[k]ocyte antigens to MHC molecules). Peptide libraries

of undecapeptides with substitutions at variable positions are prepared synthetically, and binding of the peptides to human leukocyte antigen DRB1 is used as a "immunogenicity filter" to determine variant peptide immunogenicity." Page 6, second paragraph of the present Office Action.

The Office Action states Abrams et al teach "that to modify MHC binding reactivity of peptides, rational targeted substitution of amino acid residues can be introduced to peptide ligands for regulation of immunogenic responses (p.89)." Page 6, second paragraph of the present Office Action.

With respect to the present invention, the Examiner has correctly distinguished the above-cited cases that neither of the references use an *in silico* method for generating or testing the resulting sequences. Additionally, the cited references do not utilize a computational method for generating a set of primary variant amino acid sequences either prior to application of the computational immunogenicity filter. None of the cited references discloses, suggests or teaches how to modulate immunogenicity of a protein. See Specification at page 7, lines 14-23; beginning on page 15, line 33, ending on page 16, line 5; page 20, lines 4-19; page 30, lines 1-35; beginning on page 31, line 30, ending on page 32, line 4 and page 32, lines 15-24.

The Office Action also states Altuvia et al, Meister et al, and Buus et al describes the use of "computerized algorithms to predict binding of peptides to MHC molecule."

In contrast, the present invention is directed to the method using in combination *in silico* steps for modulating the immunogenicity of a target protein comprising inputting a protein backbone structure with variable residue positions of a target protein into a computer, computationally generating a set of primary variant amino acid sequences, and applying a computational immunogenicity filter against the primary variant sequences to identify at least one candidate variant protein. It is well established that variant proteins may be generated and optimized by a methodology using computational algorithms. See for example Specification at page 20, lines 4-19; page 24, lines24-36; page 25, lines 1-30. See also US Patent Nos. 6,188,965; 6,269,312 and 6,403,312 describing methods for protein design and optimization.

The present invention uses these well-established methods in combination with a computational immunogenicity filter to modulate the immunogenicity of target proteins. See Specification at page 30, lines 15-21; page 31, lines 1-19; page 31, lines 21-29; and page 32, lines15-34.

Finally, the Office Action states, "Further, in regard to method of generating of candidate peptides, computerized way of generating peptide in the claimed method does not render the referenced methods utilizing chemical preparation of the peptides. Alternatively, computerized methods of generating peptide libraries with substitutions at variable positions proved to be an efficient way of modeling peptides which are further assessed for their biological functions." Citing Mayo et al WO 98/47089 and US Patent No. 6,269,312.

Applicants respectfully submit that the cited reference may be distinguished because there is no suggestion, disclosure or teaching of a method for modulating the immunogenicity of a protein using a computational immunogenicity filter, as specifically recited in the claims.

None of the cited references expressly or inherently describes all of the elements of the rejected claims. Therefore, Applicants submit that none of the cited references anticipates all the elements of the rejected claims.

With respect to the rejection of the claims under 35 USC §103(a), to establish a *prima facie* case of obviousness, three basic criteria must be met: 1) suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify or combine reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art reference must teach or suggest all the claim limitations. (See MPEP §2142). "A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert denied, 469 U.S. 851 (1984)."

With respect to the first criterion, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify or combine reference teachings. The Examiner acknowledges that both Fleckenstein and Abrams generate and test their variants in experimental conditions and that there is no suggestion, teaching or other disclosure of *in silico* generation or optimization of a set of protein sequences and additional application of an immunogenicity filter to the resulting set of protein sequences. Thus, even the combination of Fleckenstein and Abrams with the two Mayo et al. references would result in Applicants' invention as claimed.

Additionally, the Office Action states that there are numerous publications that describe the use of computerized algorithms to predict binding of peptides to MHC molecules, citing Altuvia, et al, Meister et al, and Buus, et al. The Office Action further states, "Thus, it would have been *prima facie* obvious to one skilled in the art to be motivated to substitute experimental determination of the immunogenicity of the candidate variant peptides with computerized estimates of their immunogenicity." See page 6-7 of the Office Action.

Applicants respectfully submit that, "because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a prima facie case of obviousness without some objective reason to combine the teaching of the references." Citing *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). "The level of skill in the art cannot be relied upon to provide the suggestion to combine references." Citing *Al-site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999). See MPEP §2143.01

One of ordinary skill would understand the cited references does not suggest, teach or otherwise disclose the use of a rational computational design algorithm in combination with a computational immunogenicity filter, as used in the instant application. Therefore, the first prong of the analysis has not been met.

The prior art reference must teach or suggest all the claim limitations. As discussed above, none of the prior art references teaches or suggests all the claim limitations of the present invention. As discussed above, there is no disclosure of: 1) a method using combination *in silico* steps for modulating the immunogenicity of a target protein comprising inputting a protein backbone structure with variable residue positions of a target protein into a computer, computationally generating a set of primary variant amino acid sequences, and applying a computational immunogenicity filter against the primary variant sequences to identify at least one candidate variant protein; or 2) the use of an *in silico* method for generating or testing the resulting sequences; and 3) use of a computational method for generating a set of primary variant amino acid sequences either prior to or after application of a computational immunogenicity filter.

None of the cited references suggest, nor would motivate, one skilled in the art to combine the cited references to produce the claimed invention.

Thus, the combined teachings of Fleckenstein et al, Abrams et al in view of Altuvia et al, Meister et al, and Buus et al and Mayo et al do not render claims 1-17 obvious. Applicants respectfully submit, in light of the foregoing discussion, none of the references either alone or in combination supports a finding that a *prima facie* case of obviousness has been established against the claims and request the rejection be reconsidered and withdrawn.

Attached hereto is a marked-up version of the changes made to the claims by the "Amendment". The attached page is captioned **"Version with markings to show changes made."** Additionally, a page captioned **"Appendix of Pending Claims"** has been attached for the Examiner's convenience. Please direct any calls in connection with this application to the undersigned at (626) 737-8019.

Respectfully submitted,

Dated: July 9, 2003

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By: _____

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VERSION TO SHOW CHANGES MADE

1. (Amended)A method for modulating the immunogenicity of a target protein, said method comprising:

a) inputting a protein backbone structure with variable residue positions of a target protein into a computer;

b) computationally generating a set of primary variant amino acid sequences using at least one scoring function; and,

c) applying a computational immunogenicity filter against said set to identify at least one candidate variant protein.

6. (Canceled in this Response)

7. (Amended) A method according to claim [6] 1 wherein said set of primary variant amino sequences optimized for at least one scoring function comprises the globally optimal protein sequence.

8. (Amended) A method according to claim [6] 1 wherein said scoring function is selected from the group consisting of a van der Waals potential scoring function, a hydrogen bond potential scoring function, an atomic salvation scoring function, an electrostatic scoring function and a secondary structure propensity scoring function.

APPENDIX OF PENDING CLAIMS

1. (Amended)A method for modulating the immunogenicity of a target protein, said method comprising:

a) inputting a protein backbone structure with variable residue positions of a target protein into a computer;

b) computationally generating a set of primary variant amino acid sequences using at least one scoring function; and,

c) applying a computational immunogenicity filter against said set to identify at least one candidate variant protein.

2. A method according to claim 1 further comprising testing said candidate variant protein to determine if said immunogenicity is altered relative to said target protein.

3. A method according to claim 1 further comprising classifying each variable residue position as either a core, surface or boundary residue.

4. A method according to claim 1 wherein said computationally generating step comprises a DEE computation.

5. A method according to claim 4 wherein said DEE computation is selected from the group consisting of original DEE and Goldstein DEE.

6. (Canceled)

7. (Amended) A method according to claim 1 wherein said set of primary variant amino sequences optimized for at least one scoring function comprises the globally optimal protein sequence.

8. (Amended) A method according to claim 1 wherein said scoring function is selected from the group consisting of a van der Waals potential scoring function, a hydrogen bond potential scoring function, an atomic salvation scoring function, an electrostatic scoring function and a secondary structure propensity scoring function.

9. A method according to claim 1 wherein said computationally generating step includes the use of a Monte Carlo search.

10. A method according to claim 1 wherein said target protein is from a non human species and said candidate variant protein exhibits reduced immunogenicity in humans.

11. A method according to claim 1 wherein the immunogenicity of said candidate variant protein is reduced relative to said target protein.

12. A method according to claim 1 wherein said candidate variant protein is non-immunogenic.

13. A method according to claim 11 or 12 wherein said candidate variant protein is more stable than said target protein.

14. A method according to claim 1 wherein said modulating the immunogenicity of said target protein comprises modifying the amino acid sequence that binds to an MHC molecule.

15. A method according to claim 14 wherein said MHC molecule belongs to MHC class I.

16. A method according to claim 14 wherein said MHC molecule belongs to MHC class II.

17. A method according to claim 1 wherein said modulating the immunogenicity of said target protein comprises modifying an amino acid sequence encoding a T cell epitope.